Satellite Symposium - Dopamine: New trends in receptor research and therapeutic implications

Dopamine receptor diversity: perspectives from new molecular and pharmacological developments.
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Five distinct dopamine (DA) receptors, named D1-D5, are expressed in the central nervous system where they control motor function, emotional states, and endocrine physiology. The D1 and D2 receptors are most abundant, and play an important role in control of voluntary movement. Expression patterns of the D3, D4, and perhaps D5 receptors, however, suggest that they may be appropriately located to mediate the effects of DA on affective, emotional, and cognitive function.
In this introduction I will discuss the molecular and pharmacological aspects of DA receptor diversity ranging from nucleotide sequences to behavioral aspects of DA receptor knockout mice. In addition I will briefly describe our recent studies on the D4 receptor, which have involved the development of selective D4 receptor agonists and antagonists, as well as a new monoclonal antibody to the human D4 receptor. My aim is to provide a short overview of this rapidly expanding area of research with important implications for both human behavior and human diseases including Parkinson's and schizophrenia.

A POTENTIAL ROLE OF 5-HT$_2$ AND D$_2$ RECEPTOR INTERACTION IN THE ATYPICAL ANTIPSYCHOTIC ACTION OF THE NOVEL SUCCIMIDE DERIVATIVE, PEROSPIRONE (SM-9018). Y. Ohno, K. Ishida-Tokuda, T. Ishibashi, H. Sakamoto, R. Tagashira, T. Horisawa, K. Matsumoto and M. Nakamura. Discovery Research Laboratories II, Sumitomo Pharmaceuticals, Konohana-ku, Osaka 554, Japan.

Patients with schizophrenia show diverse symptoms including the positive symptoms (e.g., hallucination and delusion), negative symptoms (e.g., apathy and social withdrawal) and dysphoric mood disturbances (e.g., anxiety and depression). Based on the hypothesis that dysfunction of the central serotonergic, as well as the dopaminergic, system is involved in the etiology of schizophrenia, we have developed the novel succimide derivative, perospirone, as the serotonin-dopamine antagonist (SDA)-type antipsychotic agent. This presentation will review the pharmacological profile of perospirone in comparison with other typical and SDA antipsychotics and discuss the potential role of 5-HT2 and D2 receptor interaction in the atypical antipsychotic actions of SDAs based on our findings with selective 5-HT2 antagonists. Our study revealed that perospirone, like other SDAs, differs from the typical antipsychotics by exhibiting 1) putative anxiolytic and/or antidepressant actions in various animal models, 2) reduced extrapyramidal side effects (EPS) liability (e.g., catalepsy and bradykinesia induction), 3) lower propensity to block the striatal D2 receptors as revealed by the c-fos expression and dopamine turnover and 4) weaker actions in inducing supersensitivity of dopamine receptors after repeated treatments (e.g., oral dyskinesia model). The 5-HT2 antagonists mimicked the action of perospirone in animal models of mood disorder, and could attenuate the EPS induction, striatal c-fos expression and dopaminergic sensitization associated with the D2 antagonist treatments. These findings suggest that the blockage of 5-HT2 receptors may contribute to broad efficacy profile of SDAs (i.e., antipsychotic and mood stabilizing actions) and may counteract the striatal D2 receptor blockade by antipsychotics to reduce EPS.

DOPAMINE RECEPTOR SUPERSENSITIVITY. Richard M. Kostrzewa and *Ryszard Brus. Department of Pharmacology, Quillen College of Medicine, East Tennessee State University, Johnson City, TN 37614, USA and *Department of Pharmacology, Silesian Academy of Medicine, 41-808 Zabrze, Poland.

Dopamine (DA) receptor supersensitivity (DARSS) is a phenomenon that is represented by disproportionate generation (inhibition) of second messengers and/or exaggerated behavioral responses to an agonist. Using rats in which DA D_1- or D_2-complex receptors were sensitized during ontogeny, we used behavioral indices to demonstrate that some D_1 agonist-induced effects (vacuous chewing) are dependent on the (a) presence of serotonin (5-HT) nerves, (b) supersensitization of 5-HT_2 receptors, and (c) functional muscarinic receptors. The haloperidol-induced high level of vacuous chewing in DA-lesioned rats is found to be more readily attenuated by 5-HT_2-blockers, than D_1- or D_2-blockers. DA D_3-associated quinpirole-induced yawning is modulated by substances acting at nicotinic receptors. These and associated findings by others lead to the suggestion that DARSS is a phenomenon that may be related to a facilitated neural pathway, not necessarily to a process that is restricted to neurons on which DA receptors reside.

Dopamine and reward
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Not received

IMMUNHISTOCHEMICAL DETECTION OF THE DOPAMINE TRANSPORTER IN FISH AND MARMOSET RETINAE U.D. Behrens[1], R.H. Douglas[2], H.-J. Wagner[1] Anatomisches Institut, Universität Tübingen, FRG, Department of Optometry, City University London, UK[2]

In vertebrate retinae, dopamine (DA) plays an important role in the transition from scotopic to photopic vision. At the cellular level, release mechanisms have been well described, but knowledge of DA removal from the extracellular space is scarce in the retina. We have used an antiserum against a dopamine transporter (DAT) to identify sites involved in DA reuptake in fish and marmoset retinae. DAT-immunoreactivity (DAT-ir) was investigated using a rat monoclonal DAT antibody generated against the N-terminus of the human DAT. Cryosections of paraformaldehyde fixed tissue were used for DAT-immunohistochemistry. In marmoset retinae, DAT-ir was observed in a prominent single band of processes in the distal sublayer of the inner plexiform layer, less pronounced in a small strip at the level of outer plexiform layer and in individual cells in the inner nuclear layer. The staining pattern for DAT-ir shows a nearly 100 % colocalisation with TH-ir, indicating a neuronal localisation of DAT. In cyprinid and cichlid retinae prominent DAT-ir was associated with horizontal cell bodies and with a lamination at S2, S4 and S5 of the inner plexiform layer. A partial colocalisation of DAT-ir with TH-ir is noted for the OPL and horizontal cell region labelling in the distal retina and for S5 of the IPL in the proximal retina. The distribution of DAT-ir in the inner plexiform layer of marmoset retinae coincides with the pattern of ramification of tyrosine hydroxylase-ir. A partial mismatch between immunocytochemical distribution of DAT and TH in fish retina is recognised for the DAT-staining of S2 and S4 of the IPL, indicating that additional cells may have the dopamine carrier. The staining pattern of DAT-ir in fish retina suggest a neuronal and glial localisation of the monoamine transporter, and supports the hypothesis of a heterogenous system for the termination the dopaminergic transmission.

DOPAMINE D_4-LIKE RECEPTORS IN VERTEBRATE RETINA
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Dopamine (DA) is a principal catecholamine in vertebrate retina; it is synthesized by a some amacrine or interplexiform cells. Synthesis and release of retinal DA is stimulated by light, and this suggests the amine plays a role of a light-adaptive signal. Biological actions of DA are mediated via D1- and D2-family DA receptors. D_4-DA receptor is a member of D2-receptor family, and there is a suggestion that it may be localized to photoreceptor membrane. We demonstrated in avian retina that DA D_4-like receptors negatively regulate induction of serotonin N-acetyltransferase (NAT), the rate-limiting enzyme in melatonin biosynthesis. Supporting data are as follows: *1.* nocturnal NAT activity of retina is inhibited by exposure of animals to light at night, and this light's suppressing effect can be mimicked by DA, and other DAergic drugs: quinpirole > apomorphine = pergolide > LSD-25 > (±)-ADTN > bromocriptine > SKF38393 (inactive). *2.* nocturnal retinal NAT-suppressing effect of quinpirole can be antagonized by D2-family DA receptors blockers: spiroperidol > YM-09151 > sulpiride > clozapine > UH-232 > haloperidol > domperidone >> butaclamol > raclopride, remoxiopride (inactive). *3.* comparatively high levels of mRNA encoding D_4-type DA receptor has been found in retinas of different vertebrates. We suggest that the D_4-like DA receptor regulating NAT in avian retina may be a useful model with which to study the affinity of potantial D_4-selective ligands.

MULTIPLE ROLES OF DOPAMINE IN RETINAL FUNCTION
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Dopamine is a neurotransmitter and neuromodulator that is secreted from retinal amacrine and interplexiform cells. The mode of action of dopamine differs from that of classical neurotransmitters in that it can diffuse long distances within the retina from its site of release to receptors on target cells. Dopamine acts on all neuronal cell types in the retina, including photoreceptor, horizontal, bipolar, amacrine and ganglion cells, as well as on the retinal pigment epithelial cells. Dopamine appears to play numerous roles in retinal and ocular function, and a few examples of these roles will be reviewed. During development, retinal dopamine has been implicated in ocular growth and development, and decreases of dopaminergic activity have been associated with development of experimental myopia in birds and primates. Dopamine regulates various aspects of rhythmic metabolism in the photoreceptor pigment epithelial complex, including photoreceptor disk shedding, photomechanical movements, and regulation of melatonin biosynthesis by photoreceptor cells. Retinal dopamine also appears to be involved in output pathways that regulate the synthesis of melatonin in the pineal gland. These actions of dopamine are mediated through dopamine receptor subtypes and cyclic AMP signaling pathways. In addition, dopamine receptors in retina may also regulate calcium signaling pathways via a variety of coupling mechanisms.

BRAIN DOPAMINE MECHANISMS: POTENTIAL IMPLICATIONS OF NEW FINDINGS FOR TREATMENT OF NEUROPSYCHIATRIC DISORDERS
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In terms of neurobiological and neuropharmacological aspects of dopamine (DA) neurotransmission there are several areas of particular importance e.g. schizophrenia, basal ganglia disorders and drug abuse. Notably, the changes in function of the mesolimbic DA system might facilitate the behavior associated with the reinforcing effects of drugs and contribute to drug seeking behavior. In terms of the interactions between DA and other neurotransmitter and neuromodulatory systems of particular interest are glutamate NMDA receptor complex and nitric oxide (NO). Glutamate acting through the NMDA receptor has been proposed to exert an inhibitory action on DA release while the NO donors (e.g. sodium nitroprusside) have been shown to stimulate DA release in the brain.

Recently, we have found that the catalepsy induced by a non-selective D-2 receptor antagonist haloperidol was markedly reduced by the NO donors such as molsidomine and L-arginine. On the other hand, N-nitro-L-arginine, the NO synthase inhibitor potentiated the catalepsy produced by haloperidol. Interestingly, N-nitro-L-arginine alone produced long-lasting cataleptogenic effect in rats. It appears, therefore, that NO system is involved in DA-mediated behavior thus suggesting that NO donors would be potential drugs in the treatment of neuroleptic-induced parkinsonism and at least certain symptoms of Parkinson's disease.